

**Amsterdam Gastroenterology and Metabolism**

# **AG&M**

**Annual report 2017**





## Colophon

### Pictures:

Mark van den Brink: [www.markvandenbrink.nl](http://www.markvandenbrink.nl)

Yvonne Compier: [www.yvonnecompier.nl](http://www.yvonnecompier.nl)

Jan Pauls: [www.jan-pauls.de](http://www.jan-pauls.de)

Digidaan: [www.digidaan.net](http://www.digidaan.net)

### Graphic design and layout:

Studio GoedZo: [www.studiogoedzo.nl](http://www.studiogoedzo.nl)

### Coordination:

Eva Dirkx-Beuling

Gerd Bouma

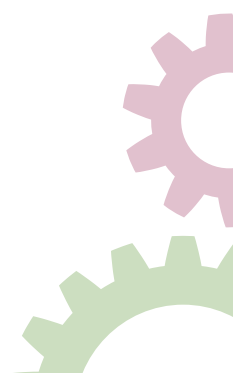
Stan van de Graaf

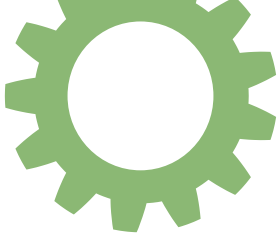
### Website:

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# Mission, vision and role of the AG&M research institute

**We have to sustain our daily energy expenditure by the efficient digestion and metabolism of our diet. The body's machinery required to manage this task is one of the most important organ systems burdened by disease in the Western world. Diet induced obesity, diabetes, cancer and chronic inflammatory diseases of the gastrointestinal tract, pancreas and liver are some of the major illnesses that affect our society. Many of these diseases seem to be associated with a Western diet and lifestyle. Inborn errors of metabolism cause rare diseases that require specialized care but also offer a unique opportunity to study human metabolism in health and disease.**

**As of January 2017, the Amsterdam Gastroenterology and Metabolism (AG&M) research institute unites the research at the Amsterdam UMC (locations AMC and VUmc) involved at the intersection of nutrition, microbiology, digestion, endocrinology and metabolism. Together, we aim to make an important contribution to improve gastrointestinal, endocrine and metabolic health and reduce the burden of disease.**

## Mission

The AG&M mission is: *'to perform research that promotes healthy nutrition and metabolism, prevents or cures gastrointestinal, endocrine and inherited and acquired metabolic disease and improves the outcomes of our patients.'*

The researchers in the AG&M institute closely collaborate with external academic and commercial parties to perform research with a true impact on the current state-of-the-art in dedicated research programs. This impact is achieved at three important levels:

1. Making fundamental discoveries of the mechanisms that maintain organ homeostasis in health and the way these are deregulated in disease.
2. Translating the revolutionary advances made in molecular biology to modern medicine.
3. Performing clinical research that truly improves our current algorithms for disease prevention and cure.

## Vision

The AG&M vision and 2020 goal is: *'to add value to our research by joining the AMC and VUmc research in gastrointestinal, endocrine and metabolic health and disease into a single research organization with 4 connected research programs.'*

Within these research programs we aim to belong to the top of the international basic, translational and clinical research in our field by contributing to important scientific advances and improving health and limiting the impact of disease in our focus areas.

## Role of the institute

The AG&M institute is designed as a network and lobby organization that promotes the quality of gastroenterology, endocrinology and metabolism research at the Amsterdam UMC. Most efforts are devoted to improving the research that is already at the top of the international academic level throughout the translational research chain. In addition, strategic areas are identified that require investment in terms of funding and/or recruitment of excellent researchers to stay at the forefront of international research. The institute focusses on identifying, recruiting and supporting talent from the level of the early career stage.

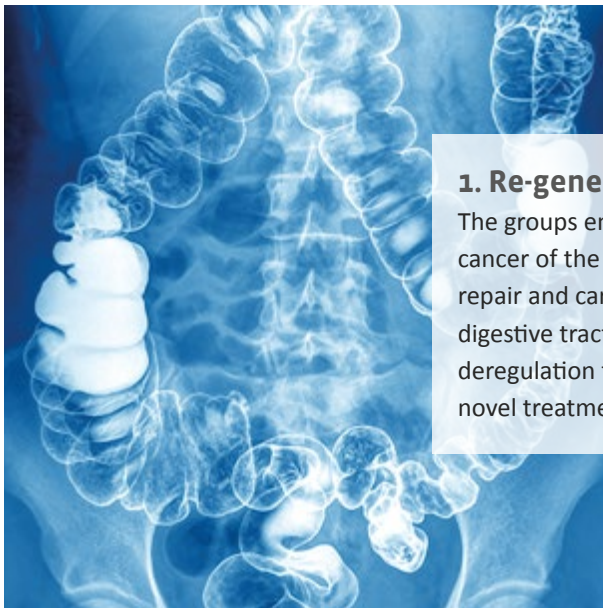
In this annual rapport of 2017, the first year of the AG&M existence, is described how considerable time and resources have been devoted to build a foundation necessary to develop and improve the quality of the AG&M institute.

The AG&M events (Kick-off party, AG&M retreat, AG&M symposium, AG&M Tager Lectures) and grants were organized in a manner to familiarize the researchers of the Amsterdam UMC with each other and promote the quality of gastroenterology, endocrinology and metabolism research at the Amsterdam UMC.



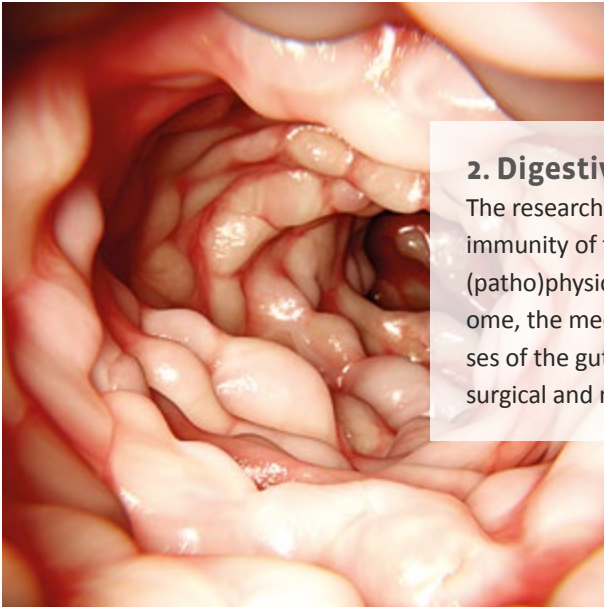
# AG&M Research Programs

Based on an inventory of the strengths of the research in gastroenterology, endocrinology and metabolism conducted at the Amsterdam UMC, four research programs have been specified:



## **1. Re-generation and cancer of the digestive system**

The groups embedded in the research program “Re-generation and cancer of the digestive system” focus on the postnatal development, repair and carcinogenesis, and functionality and motility of the digestive tract. The physiological homeostasis of the digestive tract, the deregulation thereof in the oncogenic state, and the development of novel treatment strategies are important areas of study.



## 2. Digestive immunity

The research program “Digestive immunity” focusses on the mucosal immunity of the human digestive system in health and disease. The (patho)physiology of the digestive immunity, the relation to the microbiome, the mechanism of action of therapies of immune mediated diseases of the gut, pancreas and liver, nutrition and the development of novel surgical and medical treatment strategies are the main research areas.

## 3. Endocrinology, metabolism and nutrition

In the research program “Endocrinology, metabolism and nutrition”, the effect of lifestyle, diet and malnutrition on metabolism and hormonal regulation plays a central role. The ultimate aim of this research program is to improve metabolic health of patients with metabolic and endocrine pathologies.



## 4. Inborn errors of metabolism

Within the research program of “Inborn errors of metabolism” the research groups investigate rare inborn errors of metabolism manifesting from the (pre)neonatal period into adulthood. To unravel the cause of a metabolic derangement in patients suspected of a genetic metabolic disorder and to develop and improve treatment for patients with a genetic metabolic disorder are the main areas of focus in this research program.



## Meet the AG&M Research Board

The AG&M research board consists of two AG&M directors, five members (at least one representative from each of the four AG&M research programs) and a secretary. The research board meets once per two months and discusses the AG&M policy.



## AG&M directors



### Prof. dr. Gerd Bouma

Department of Gastroenterology and Hepatology

*Professor of Gastroenterology and Hepatology  
Group leader & AG&M Co-Director VUmc*

**Specialization:** Gastroenterology

**Research subject:** Mucosal immunology.

#### *What I want to achieve with the AG&M research institute...*

I hope to strengthen collaborations between researchers from different disciplines and the two locations of Amsterdam University Medical Centers, VUmc and AMC. The AG&M research institute has the unique position to act as a network for all researchers in fields bordering gastroenterology, endocrinology and metabolism. In addition to those collaborations, translational research is at the core of AG&M and we strive to bring together clinical scientists and basis researchers. After empowering our own researchers and the young research talent within our institute, I ultimately hope to shape AG&M into a strong national and international brand.



### Dr. Stan van de Graaf

Tytgat Institute for Liver and Intestinal Research &  
Department of Gastroenterology and Hepatology

*Associate professor*

*Group leader & AG&M Co-Director AMC*

**Specialization:** Biochemistry/Physiology

**Research subject:** Targeting bile acid transport proteins to treat metabolic diseases and cholestasis.

#### *What I want to achieve with the AG&M research institute...*

In the coming years I want to stimulate collaborations between people with different scientific expertise. AG&M has a unique multidisciplinary character that will allow our researchers to find novel treatment options, new insight into disease etiology and/or novel fundamental knowledge. Such productive synergy should be facilitated and encouraged as much as possible with minimal bureaucracy. AG&M fulfills this facilitating role and defends the interests of its researchers within the Amsterdam University Medical Centers and beyond and will increasingly do so. Researchers within AG&M should feel connected to (and at home within) the AG&M scientific network of people and able to find out-of-the-box solutions (ideas, tools, expertise) with other AG&M researchers. To realize this it is important that people meet, for example at the annual retreat, symposia and meetings that are organized within AG&M to learn about the extensive expertise and tools available within the institute. AG&M harbors a lot of talent and the institute can help them to develop further. Furthermore, to recruit external talent the AG&M institute should become (inter)nationally recognized as a leading institute in gastroenterology, endocrinology and metabolism.

## AG&M Research Board members



### Prof. dr. Max Nieuwdorp

AMC and VUmc Internal Medicine

*Professor of Internal Medicine, with a special focus on diabetes mellitus*

*Head of the department of Experimental Vascular Medicine*

*AG&M Research Board member*

**Specialization:** Internal medicine: Endocrinology

**Research subject:** The role of gut microbiota in development of human obesity, insulin resistance and dyslipidemia.

#### *What I want to achieve with the AG&M research institute...*

Working since several years with several talented (MD)PhD students and postdocs in the field of translational diabetes at both AMC and VUmc, I aim to further integrate both translational and clinical researchers in adherent research fields within AG&M (eg Gastroenterology Tytgat institute) and other research school (like AI&I and ACS). To this end, together with Prof. Joost Wiersinga (I&I) and Prof. Wouter de Jonge (AG&M) we have founded the AMC gut microbiota platform in 2016. This platform (comprising of a dedicated technician, bioinformatician as well as MiSeq) aims to help other researchers at AMC-VUmc to integrate microbiota analyses in their (animal and human) experiments.



### Dr. Riekelt Houtkooper

Laboratory Genetic Metabolic Diseases

*Scientific staff member (UHD)*

*Principal investigator at Laboratory Genetic Metabolic Diseases*

*AG&M Research Board member*

**Specialization:** Biochemistry/Physiology

**Research subject:** Mitochondrial metabolism in health and disease. Metabolic aging.

#### *What I want to achieve with the AG&M research institute...*

The multidisciplinary research environment of AG&M, which covers both basic, translational and clinical science, proves a fertile breeding ground for new ideas and collaborations. In the years to come I aim to establish AG&M even more as a leading research institute for metabolic and gastrointestinal research. Implementing state-of-the-art technologies in facilities, and supporting and/or recruiting talented junior PIs are among my top priorities to sustain our high-quality research and realize our ambitions.



**Prof. dr. Louis Vermeulen**

Center of Experimental and Molecular Medicine

*Professor of Molecular Oncology*

*Principal investigator at Center of Experimental and Molecular Medicine*

*AG&M Research Board member*

**Specialization:** Molecular oncology; colorectal cancer

**Research subject:** Molecular subtype specific stem cell dynamics in developing and established colorectal cancers.

***What I want to achieve with the AG&M research institute...***

The AG&M research institute provides a great platform to promote excellence in science and medical care. The joint talents and resources of the AMC and VUmc will result in a world-class research institute in the fields of Endocrinology, Gastroenterology, and Metabolism. This combination of research areas is unique and provides important opportunities for innovation for example in the role of nutrition in medicine, novel strategies to combat welfare disease such as diabetes, and prevention of gastroenterological malignancies. Personally I aim to achieve optimal integration of AMC and VUmc research in the area of gastrointestinal cancers and stem cell sciences in the themes covered by the AG&M. Furthermore, I will actively promote young research talent within the institute to provide them with the opportunities to advance their careers and to enable them to importantly contribute to the central aims of our institute.



**Dr. Anje te Velde**

Tytgat Institute for Liver and Intestinal Research & Department of Gastroenterology and Hepatology

*Principal investigator at Tytgat Institute for Liver and Intestinal Research*

*AG&M Research Board member*

**Specialization:** Immunology

**Research subject:** Study of chronic intestinal inflammation (inflammatory bowel disease, IBD): pathophysiology and therapeutic interventions.

***What I want to achieve with the AG&M research institute...***

As a biomedical researcher with a multifaceted interest and experience I participate with great enthusiasm in a board with a broad mission to stimulate research that promotes healthy nutrition and metabolism. In the Western society chronic non-communicable diseases are linked to the Western diet and lifestyle and need to be studied with a multidisciplinary approach where cooperation and communication are indispensable pillars for sharing knowledge. AG&M is the vehicle that can organize the network, communication and lobby necessary to direct this excellent research in the Amsterdam UMC.



### Prof. dr. Gajja Salomons

Metabolic Laboratory & Department of Genetic Metabolic Diseases

*Professor of Molecular Biology of  
Neurometabolic Disorders*

*Head of the Metabolic Laboratory (Location VUmc) and  
as of 1.1.2018 Head of Department of Genetic Metabolic  
Diseases (Location AMC)*

*AG&M Research Board member since 9.2016.*

**Specialization:** Clinical laboratory geneticist, (inborn errors of) metabolism

**Research subject:** Inborn errors of metabolism with a focus on neurometabolic disorders including white matter disorders.

#### *What I want to achieve with the AG&M research institute...*

- that the AG&M members consider our institute as a valuable and inspiring network for (young) scientists and clinicians. This will initiate new connections not only between scientists of diverse disciplines but also between those working on both locations of Amsterdam UMC. Such connections will result in novel (inter)national collaborations and exciting translational research.
- that investigators from both locations will actively apply and profit from the (young) investigator grants.
- that the AG&M members/members of the other research institutes and/or Amsterdam UMC employees will find the Metabolic Laboratories as a landmark if they are interested in our expertise and seek collaboration on metabolism and/or wish to make use of our facilities (e.g. (un)targeted metabolomics, lipidomics, model systems).

## AG&M office



### Dr. Eva Dirkx-Beuling

Amsterdam Gastroenterology & Metabolism (AG&M)

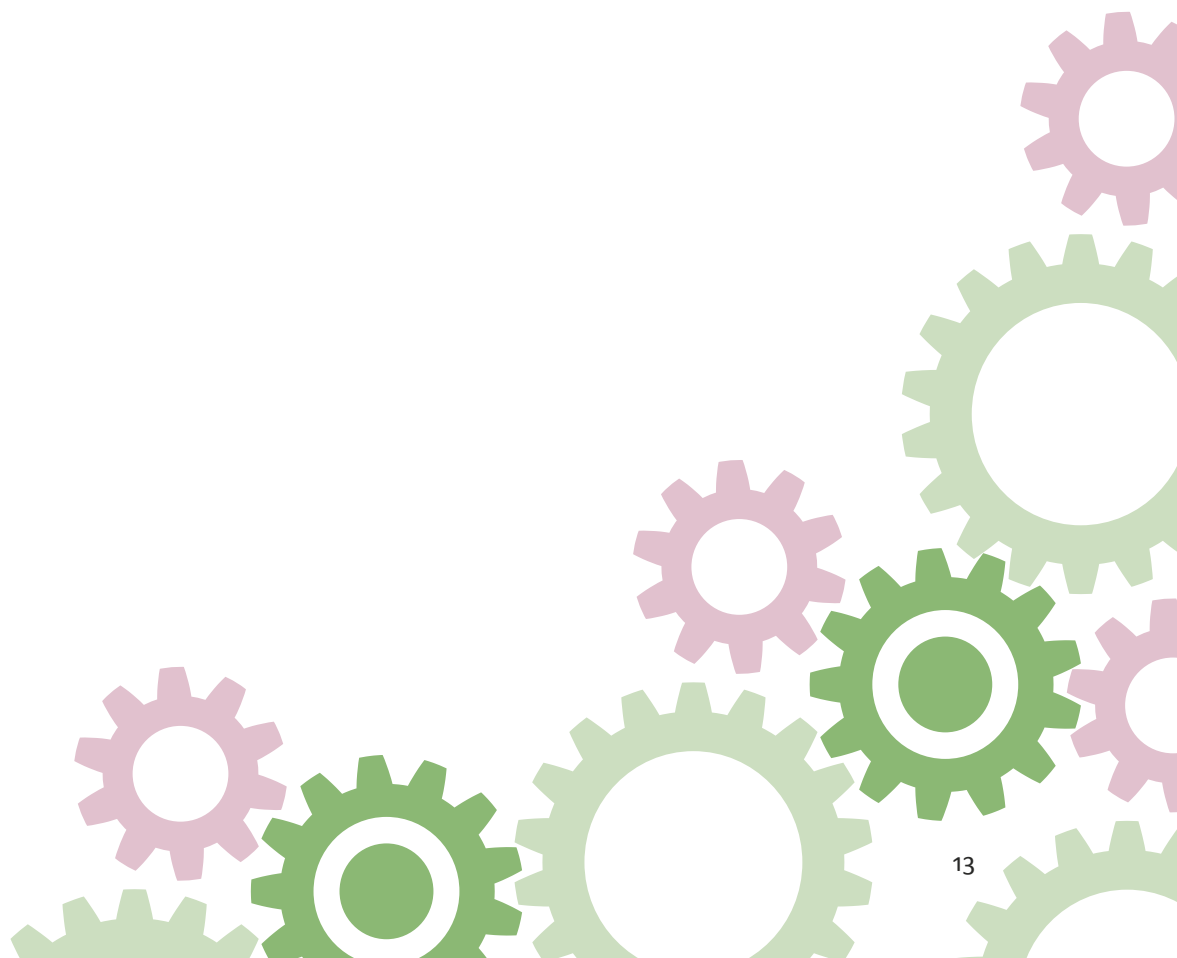
*Policy officer AG&M*

*Secretary AG&M Research Board*

**PhD-thesis:** GATA transcription factors and the regulation of intestinal development, differentiation and function.

#### *What I want to achieve with the AG&M research institute...*

My goal for the AG&M research institute is to create a foundation and facilitate the necessities that allows the AG&M researchers to achieve the AG&M's mission: *“to perform research that promotes healthy nutrition and metabolism, prevents or cures gastrointestinal, endocrine and inherited and acquired metabolic disease and improves the outcomes of our patients.”* To be able to achieve this mission, AG&M researchers should feel involved and at home at the institute, should know and trust each other, should work with and learn from each other and should have access to all the necessary resources.





# AG&M Science Impressions 2017

To give an impression of the research conducted in the AG&M research institute, seven couples of young investigators and their supervisors were invited to present the research projects they worked on in 2017.

## The importance of pressure-impedance analysis in children with swallowing disorders

**Thesis:** Pediatric Gastroesophageal Motility Disorders - Diagnostic Possibilities and Pitfalls. M.M.J. Singendonk  
*Maartje Singendonk and Marc Benninga*

### Treatment of functional gastrointestinal conditions

Prof. dr. Marc Benninga is the head of the Pediatric Gastrointestinal department of the Emma Children's Hospital AMC. After his pediatric training, Benninga performed research at The Women's and Children's Hospital, Adelaide, Australia with Prof. dr. Geoff Davidson and Assistant Prof. Taher Omari. Marc Benninga's current research focuses on functional gastrointestinal conditions such as gastro-oesophageal reflux disease, chronic abdominal pain, constipation and fecal incontinence. He has now supervised over 40 PhD students and has coordinated and executed large-scale clinical therapeutic trials to evaluate new medicines and nutritional supplements such as pre- and probiotics. In 2010, he obtained two grants for over €700,000 from ZonMw's Health Care and Efficiency Research Program, to study the effectiveness of hypnotherapy in the treatment of children with chronic abdominal pain and the effectiveness of hypnotherapy in the treatment of adolescents and adults with inflammatory bowel disease in remission and irritable bowel syndrome.

### Pediatric gastro-oesophageal motility disorders

In 2013, Maartje Singendonk conducted a study to develop a diagnostic tool for the evaluation of infant gastro-oesophageal reflux disease in the group of Prof. Benninga as part of her medical training. After this internship, Prof. Benninga offered her a position as a PhD candidate. As her research would focus on the pathophysiology and treatment of gastro-oesophageal motility disorders, Prof. Benninga organized her visit to the motility unit of The Women's and Children's Hospital in Adelaide to work with his old friend and expert in the field, Assistant Prof. Omari. Here, Maartje learned how to perform, analyze and interpret pediatric oesophageal high-resolution manometry (HRM) studies to characterize oesophageal function in the evaluation of swallowing disorders. The clinical interpretation of oesophageal HRM studies is facilitated by the Chicago Classification (CC), which provides a classification of oesophageal motility and outflow disorders, with a clear distinction between major and minor disorders of peristalsis. Despite its broad use in the adult population, there are several limitations regarding to its application for the evaluation of pediatric motility disorders.



Maartje Singendonk and Marc Benninga

First, the CC is not validated in or created for the pediatric population and pediatric normative data are lacking due to ethical considerations. Second, manometric recordings from children are harder to interpret due to a higher likelihood of multiple swallowing and artefacts as result of body movement and crying. Third, children have a shorter oesophageal length and smaller lumen diameter which may influence the derivation of HRM metrics. Together with Prof. Omari, Maartje worked on the development of age-specific analysis criteria for pediatric HRM. Although these proposed age/size adjusted CC cut-off criteria could potentially improve the diagnosis of pediatric oesophageal motility disorders, the inclusion of corroboratory evidence could further enhance the potential for a correct HRM diagnosis.

### **Pressure-impedance analysis to determine oesophageal function in children with swallowing disorders**

Intraluminal impedance can be measured in conjunction with pressure to provide additional information regarding bolus flow (i.e., high resolution impedance manometry [HRIM]), but without any additional burden for the patient. The diagnostic value of intraluminal impedance recording has been recently enhanced by the use of integrated pressure-impedance analysis. This analysis may complement routine HRM diagnosis based on the CC, as it offers the possibility to quantify degrees of pressure-flow dysfunction in relation to perception of dysphagia symptoms. A number of studies in adults support the notion that pressure-impedance is able to relate the degree of oesophageal flow resis-

tance and stasis to severity of dysphagia symptoms and altered perception of bolus passage.

In several studies, we explored the use of pressure-impedance analysis in children. First, by applying pressure-impedance analysis to a cohort of 76 pediatric patients referred for clinical HRIM, we found that children with disordered oesophageal motor patterns as defined by the CC could be stratified into abnormality based upon bolus flow-resistance characteristics and/or bolus clearance failure. In addition, patients with dysphagia symptoms were also more likely to have disordered oesophageal function.

### **Future application of pressure-impedance analysis**

In patients with dysphagia, clinical symptoms do not correlate well with conventional assessment methods of motor function such as radiology and manometry. Pressure-impedance analysis therefore has the potential to better guide the approach to diagnosis and management of oesophageal disease through objective longitudinal measurements before and after medical or surgical intervention. Our group has already explored its use in pediatric patients with achalasia and morbid obese adolescents undergoing gastric banding. Pressure-impedance analysis may in the future well be used to make rational therapeutic decisions in other pediatric patients undergoing surgery of the gastrointestinal tract, such as oesophageal atresia patients and patients with severe gastroesophageal reflux disease who require fundoplication.

## Analysis of glucocorticoids in neonatal hair increases the understanding of the developing hypothalamus-pituitary-adrenal axis

Endocr Connect 2017;6:692-699

Jonneke Hollanders and Martijn Finken

### The developing hypothalamus-pituitary-adrenal axis in preterm born infants

The pediatric endocrinology research group of the VUmc consists of Martijn J.J. Finken, pediatric endocrinologist; Joost Rotteveel, pediatric endocrinologist; Britt van Keulen, PhD student; Jonneke Hollanders, PhD student and Bibian van der Voorn, PhD student.

The Developmental Origins of Health and Disease (DOHaD) hypothesis states that adversities occurring early in life could predispose to later non-communicable diseases, such as cardiometabolic diseases and neurodevelopmental problems. The hypothalamus-pituitary-adrenal (HPA) axis may mediate these associations, given its susceptibility to early-life events as well as its long-lasting effects on metabolism and the brain.

Infants born preterm have to face many adversities early in life, while their HPA axis is still developing. In our research group, we therefore aim to characterize normal development of the HPA-axis, using sophisticated tools, in healthy subjects. We studied normal HPA-axis development by analyzing glucocorticoids (GCs) in neonatal hair, which offers a retrospective view on intra-uterine GC regulation. We are also exploring the role of GCs in breast-milk. We have discovered that breast-milk GCs follow the diurnal rhythm of maternal HPA-axis activity, and we are now researching whether this diurnal rhythm is associated with the infant's HPA-axis activity, behavior, sleep pattern, and body composition.

We are currently developing an assay to measure GC bioactivity, i.e., the effect of cortisol as well as its precursors and metabolites on the glucocorticoid receptor. In preterm infants, in whom the HPA-axis is unripe, such a tool could have the potential to predict conditions associated with GC deficiency, such as refractory hypotension and bronchopulmonary dysplasia. Moreover, many of these infants are treated

with glucocorticoids for various conditions, but such treatment may be harmful for the developing brain. Assessment of GC bioactivity, which would also measure the additional effect of GC supplementation, might offer the possibility of patient-tailored GC dosing.

We have recently demonstrated in meta-analyses that sex and age are determinants of HPA-axis activity and reactivity. Now, we are exploring this further, by studying longitudinal data of a well-characterized cohort of twins. We aim to quantify the relative contributions of genetic and environmental factors, as well the impact of age, sex, pubertal status and growth pattern, among other factors, on cortisol metabolism. This approach would allow us to calculate an individual's HPA-axis activity, so that in the near future it will become possible to tailor GC replacement therapy based on clinical parameters.

Our ultimate goal is to use these insights to provide individually-tailored care to preterm infants, to improve their short- and long-term outcome.

### Glucocorticoids in neonatal hair

Part of Jonneke Hollander's PhD-project is the publication of 2017 that concerns the measurement of GCs in neonatal hair.

Hair GCs are used as a measure for HPA-axis activity over time without the disturbing influence of the circadian rhythm. Additionally, the measurement of GCs in hair offers a retrospective view, as it reflects the exposure to GCs in the time frame during which the hair grew. We therefore aimed to study whether GCs measured in hair from neonates directly postpartum might be a useful tool to assess intrauterine HPA-axis activity.

Hair was taken from neonates (gestational age ranging from 33+5 to 42+1 weeks) and their mothers on the first day postpartum and at an outpatient visit (OPV)





Jonneke Hollanders and Martijn Finken

at around 6 weeks postpartum. Cortisol and cortisone concentrations were determined in the entire strand of hair from the neonate at birth, and in the centimeter closest to the scalp from the hair of the neonate at 6 weeks postpartum as well as both the maternal hair strands.

We found that neonatal cortisol levels, but not cortisone levels, directly postpartum as well as at the OPV were correlated to maternal cortisol levels ( $P < 0.001$ ). However, neonatal GC levels were  $>5$  times higher than maternal levels, with a decrease of  $\pm 50\%$  between birth and the OPV for cortisol, while cortisone levels remained stable. Since GC concentrations were still increased compared to maternal levels at the OPV 6 weeks postpartum, hair GC concentrations at this time point appear to reflect both the intra- and extrauterine period. Directly postpartum and at the OPV, most perinatal and maternal factors were not

associated with neonatal GC levels, or only weakly, such as birth weight in kg (but not SDS), perinatal infection and caesarian delivery. However, a striking positive association was found between neonatal GC levels postpartum and gestational age, which was also present when the analyses were repeated with only term subjects. This seems to be a reflection of the increase in cortisol concentrations during the third trimester, a phenomenon that might be caused by a positive feedback loop due to corticotrophin-releasing hormone production by the placenta. This positive feedback loop is thought to promote fetal organ maturation, and might also play a part in the induction of labor. Although the specifics of hair growth in utero are still largely unclear, it is likely that at least the third trimester is reflected in neonatal hair. Therefore, GCs measured in neonatal hair might be a useful tool to assess the intrauterine environment, which allows us to increase our understanding of the developing HPA axis.

## Hedgehog is a critical sensor of intestinal epithelial integrity

Cell Mol Gastroenterol Hepatol. 2017 Sep 5;5(1):67-82  
Florien Westendorp and Manon Wildenberg

### Inflammatory bowel diseases – Mechanisms and therapy

The research in Manon Wildenberg's group is focused on both development and treatment of intestinal inflammation. The whole process of disease is studied from the initiation of inflammation through to the wound healing and restoration process during recovery. While the onset of disease is broadly understood to be an active biological process, the resolution of inflammation has received much less attention. However, in order to restore normal tissue function upon therapeutic intervention, this is a crucial step, which involves dampening of the inflammatory response as well as remodeling and healing of the damaged intestinal tissue. In particular in patients suffering from inflammatory bowel disease (IBD) this process is often disturbed, resulting in remaining tissue damage and dysfunction as well as increased complications after intestinal surgery. We have shown that the response to anti-TNF, a medication commonly used in IBD, includes macrophages with specific wound healing properties, and that in the absence of these cells, response to therapy is strongly decreased. Interestingly, we also found that in some patients, the tissue surrounding the diseased intestine lack this type of wound healing macrophage and that these patients are at strongly increased risk of developing complications after surgery. Together these data suggest that this cell type is an interesting target for future therapeutic development.

From a more molecular viewpoint, we are studying the damage response of the intestinal epithelium itself. Under healthy conditions, the epithelium forms a strong barrier protecting the organism from the luminal content. Upon damage, this barrier function is disrupted, and the intestinal immune system needs to be activated in order to limit the consequences of exposure to potentially dangerous luminal content.

### Hedgehog acts as a critical sensor of intestinal epithelial integrity

Florien Westendorp, one of the PhD-student in Manon Wildenberg's group, investigates the role of Hedgehog in the intestine.

One of the key signaling molecules produced by the intestinal epithelium to maintain immune tolerance is the morphogen Hedgehog. Hedgehog is exclusively expressed by the intestinal epithelial layer and signals to the underlying mesenchyme. Our research group has found that Hedgehog acts as a sensor of epithelial integrity. Deletion of Hedgehog from the intestinal epithelium activates a wound healing response with epithelial proliferation and infiltration of immune cells, ultimately leading to a severe colitis with extensive fibrosis. In line, in patients with active IBD and thus epithelial damage, signaling by Hedgehog is decreased compared to healthy intestine. Furthermore, a single nucleotide polymorphism in the Hedgehog target Gli1 was found to reduce transcriptional function of the protein and predispose to IBD. In a recent study, we have focused on identifying the mesenchymal cell type responsible for the effects mediated by Hedgehog and the exact signaling pathway via which Hedgehog suppresses an inflammatory response.

Our data show that Hedgehog specifically signals to fibroblasts in the mesenchyme. Both within the small intestine and the colon, the majority of the Hedgehog responsive cells (Gli1+ cells) expresses pan-fibroblast markers such as collagen III, gp38, and PDGFR $\beta$ . When studying the anti-inflammatory role of Hedgehog, we found that short term loss of Hedgehog from the intestinal epithelium leads to a rapidly developing immune response. Within days after loss of Hedgehog in the epithelium, a strong increase in chemokine expression was observed which was accompanied by the influx of various immune cells and increased



Florien Westendorp and Manon Wildenberg

susceptibility to DSS-induced colitis. Specifically, loss of Hedgehog resulted in a strong increase in the expression of CXCL12. In vitro, we demonstrated that fibroblasts indeed secrete this chemokine, resulting in directed immune cell migration. Addition of Hedgehog to the system decreased expression of CXCL12 and consequently reduced immune cell migration.

In summary, we show Hedgehog to be a critical sensor of epithelial integrity. Upon damage, the signal is lost, resulting in increased fibroblast-derived CXCL12 and a rapid immune response. Disbalance of this system may contribute to development of excessive inflammatory responses, such as those seen in IBD.

## A new functional assay may be of added value for physicians in counseling parents of patients with specific neurometabolic disorders.

J Inherit Metab Dis. 2018 Mar;41(2):169-180

Ana Pop and Gajja Salomons

### Neuro-metabolic disorders and the development of diagnostic approaches and therapies for specific inborn errors of metabolism

Prof Gajja Salomons obtained her PhD at the Netherlands Cancer Institute/University of Amsterdam in 1998. In 2012 she became professor of molecular biology of neurometabolic disorders and head of the Metabolic Laboratory of VU University medical center as successor to Prof Cornelis Jakobs. As of 1st of January 2018 she is the new head of both this laboratory and the Department of Genetic Metabolic Diseases (successor of Prof Ronald Wanders). Both Metabolic Laboratories have a long-standing history of translational research which finds its basis in the unique in house developed (diagnostic) tests, offered worldwide to patients with suspicion of an inborn error of metabolism (IEM). This position will be further extended and used for personalized patient diagnostics. These tests and the expertise are also being used for other applications, including studies on pathophysiology, treatment follow-up and genotype-phenotype studies.

The expertise in these laboratories is concentrated on the following levels: metabolomics (metabolites in body fluids), enzymes, genetics (DNA/RNA) and is specialized in functional studies using models (to characterize genetic variants). The combined expertise on mass spectrometry, biochemistry, models and genetics is an important characteristic of these laboratories and is pivotal for the success of the overall aims.

The overall research aim of the Metabolic Laboratory location VUmc is unravelling the cause of (neuro) metabolic disorders and the development of diagnostic approaches and therapies for specific inborn errors of metabolism. The main translational research lines in this laboratory are studies on:

1. creatine metabolism and transport, for which therapies and/or newborn screening pilots are being performed;

2. 2-hydroxyglutaric acid metabolism in IEM and cancer, including the effects of IDH1 and IDH2 mutations;
3. pentose phosphate pathway function and IEM;
4. aminoacyl tRNA synthetase function and associated disorders with a focus on leukodystrophies and
5. vitamins (B1, B6, B12, folate) and one carbon metabolism. The laboratory functions as a worldwide reference laboratory for most of these disorders that belong into these research lines and is an NFU approved expertise center for creatine deficiency disorders. In the next years we will fuse both Amsterdam UMC metabolic laboratories into one flourishing center of expertise and excellence. This will not only further strengthen the research and diagnostics of the Metabolic Laboratory (location VUmc) and the department of Genetic Metabolic Diseases (location AMC) but will also create more opportunities to strengthen and initiate novel collaborations on general metabolism related to other fields. The laboratory already has many (inter) national collaborations and is actively involved in training of (inter)national students and specialists.

### Unravelling the pathophysiology of neurometabolic disorders

Ana Pop is a PhD student who obtained her University degree (biology, summa cum laude) in Romania. Ana worked at the Max Planck Institute, Jena, Germany, the Free University Amsterdam and VUmc in the innovation and development of diagnostic procedures. Currently she is finishing her PhD studies on functional characterization of several inherited (genetic) neurometabolic disorders, with a focus on unravelling the pathophysiology of several neurometabolic disorders mainly associated with Krebs cycle. Among them is the group of 2-hydroxyglutaric acidurias.



Ana Pop and Gajja Salomons

Combined D-2- and L-2-hydroxyglutaric aciduria (D/L-2-HGA) is a devastating neurometabolic disorder, usually lethal in the first years of life. Previously, we showed that autosomal recessive mutations in the SLC25A1 gene are detected in patients affected with combined D/L-2-HGA. SLC25A1 encodes for the mitochondrial citrate carrier SLC25A1 (CIC), which belongs to the SLC25 family of mitochondrial carriers. The CIC is a protein of 311 amino acids that mediates the exchange of mitochondrial citrate/isocitrate for cytosolic malate. The mitochondrial citrate is either used as an intermediate of the Krebs cycle or transported outside the mitochondria by the CIC, where it plays important roles in fatty acid and sterol synthesis, regulation of glycolysis, histone acetylation, and other physio pathological processes. When the CIC function is impaired, it is presumed that mitochondrial citrate accumulates, and as a result, cytosolic citrate concentration decreases. Indeed, as a group, the D/L-2-HGA patients showed significantly lower urinary levels of citrate compared to the control group. However, the urinary citrate levels cannot be used as a marker for individual patients.

Recently, we showed that transfection of deficient fibroblasts with wild-type SLC25A1 restored citrate efflux and decreased intracellular 2-hydroxyglutarate levels, confirming that deficient CIC is the cause of D/L-2-HGA. We developed and implemented a functional assay

and applied it to all 17 missense variants detected in a total of 26 CIC-deficient patients worldwide, including eight novel cases, showing reduced activities of varying degrees. In addition, we analysed the functional and/or structural importance of mutated residues using our existing scoring system, in collaboration with an Italian group in Bari. We reported the clinical and biochemical overview of all known D/L-2-HGA patients and provided a first observation that a genotype–phenotype correlation exists in this small cohort of patients with D/L-2-HGA. Lack of residual SLC25A1 transporter activity (severe missense mutation or truncating mutation) is likely to contribute to a severe disease presentation associated with early death. We also noted a strong positive correlation between extensive medical care and increased life expectancy, irrespective of type of mutation/residual activity.

In conclusion, our newly developed functional assay can be used, together with structural data and residue-specific scores, as an assisting tool for interpreting new missense variants and may be of added value for physicians in counselling parents of patients with (missense) variants in CIC.

Currently, Ana is studying the clinical significance of missense variants in the D2HGDH gene, responsible for another form of 2-hydroxyglutaric aciduria, D-2-hydroxyglutaric aciduria type I.

## Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial.

Lancet. 2018 Jan 6;391(10115):51-58

*Sandra van Brunschot and Paul Fockens on behalf of the Dutch Pancreatitis Study Group*

### Advanced diagnostic and therapeutic gastrointestinal endoscopy in GI

The research group of Prof. dr. Paul Fockens focuses on advanced diagnostic and therapeutic gastrointestinal endoscopy in the areas of colorectal and pancreato-biliary diseases as well as neurogastroenterology.

#### Colorectal neoplasia

In the research line of colorectal neoplasia, we focus on endoscopic detection and characterization of neoplasia as well as different ways to treat neoplasia. Additionally we focus on the national program for bowel cancer screening. Colorectal cancer screening, imaging and therapy is one of the areas of research in which we cooperate with Prof. Evelien Dekker, who is the principal investigator of this theme.

#### Pancreato-biliary diseases

The area of Pancreato-biliary diseases focuses on benign and malignant clinical issues. Current topics are:

1. incidental pancreatic cysts
2. familial pancreatic cancer
3. endoscopic therapy for necrotizing pancreatitis

The pancreato-biliary research line is overseen by Dr. Jeanin van Hooft.

#### Neurogastroenterology

New endoscopic interventions for achalasia have been developed and implemented in clinical practice. These interventions (Per-Oral Endoscopic Myotomy) are now studied in multicentre randomised controlled clinical trials under supervision of Dr. Arjan Bredenoord.

### Infected necrotizing pancreatitis

As part of her PhD-research, Sandra van Brunschot was involved in the TENSION trial; a multicentre randomised trial comparing an endoscopic and surgical step-up approach in patients with infected necrotizing pancreatitis.

Infected necrotizing pancreatitis is a potentially lethal disease that almost always requires an intervention. In recent years, the surgical step-up approach has become standard of care replacing primary open necrosectomy. A promising minimally invasive alternative is the endoscopic step-up approach. Recent years, the Dutch Pancreatitis Study Group conducted a multicentre randomised trial (TENSION) comparing an endoscopic and surgical step-up approach in patients with infected necrotizing pancreatitis.

#### TENSION trial

Patients with infected necrotizing pancreatitis were randomly assigned to the endoscopic or surgical step-up approach. The endoscopic group consisted of endoscopic transluminal drainage followed, if necessary, by endoscopic necrosectomy. The surgical group consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement (VARD). The primary endpoint was a composite of major complications (i.e. new onset organ failure, bleeding, perforation of a visceral organ, enterocutaneous fistula and incisional hernia) or death during 6 months of follow-up. Secondary endpoints included, among others, pancreatic fistula, length of hospital stay and costs.

A total of 98 patients were enrolled in 19 Dutch hospitals. The primary endpoint occurred in 22 of 51 patients (43%) in the endoscopic group and in 21 of



Sandra van Brunschot and Paul Fockens

47 patients (45%) in the surgical group (risk ratio 0.97; 95% CI 0.62 to 1.51,  $P=0.88$ ). There were no significant differences in the individual components of the primary endpoint (e.g. death 18% versus 13%;  $P=0.50$ ). There was a lower incidence of pancreatic fistula (5% versus 32%;  $P=0.001$ ) and length of hospital stay was shorter (mean 53 days (SD 47) versus 69 days (SD 38);  $P=0.01$ ) in the endoscopic group. In the endoscopic group, 22 patients (43%) as compared with 24 patients (51%) in the surgical group did not need necrosectomy after drainage as first

step of treatment. Furthermore, the difference in total mean costs was €13655 (19%, BCa 95% CI -€35,782 to €10,836) in favour of the endoscopic group.

In conclusion, the TENSION trial did not show superiority of the endoscopic step-up approach, as compared with a surgical step-up approach, in reducing major complications or death in patients with infected necrotizing pancreatitis. However, the rate of pancreatic fistula and length of hospital stay were significantly reduced.

## The effects of hormonal treatment on breast development in transgender persons

J Clin Endocrinol Metab. 2018 Feb 1;103(2):532-538  
*Christel de Blok and Martin den Heijer*

### Effects of hormonal treatment in transgender persons

One of the research programs of Prof. dr. Martin den Heijer focusses on the effects of hormonal treatment in transgender persons. Gender dysphoria is the feeling of incongruence between the experienced gender and the assigned sex at birth. Persons with severe gender dysphoria, may wish to change their body in line with their gender identity by medical treatment. Once gender dysphoria is diagnosed, the person may start with hormone treatment to acquire more masculine or feminine features, and later on, if desired, gender confirming surgery. The care of people with gender dysphoria is complex and sustained, and involves many disciplines which all cooperate within the Center of Expertise on Gender Dysphoria.

Hormonal treatment is an important part in the treatment of patient with genderdysphoria, but the scientific data on the effects and side effects are scarce. An important research question is the short and long-term effects of cross-sex hormonal treatment. This is important for an efficient and safe care for transgender people. Also it offers an unique possibility to study effects of sex hormones in general and to study the hormonal basis of sex differences.

Research is performed prospectively on short-term (up to 3 years) effects of hormonal treatment in the ENIGI study. Papers have been published on the effects on bone, body composition and on breast development (which is the work of Christel de Blok). In the Amsterdam Cohort of Genderdysphoria we study the long-term effects of hormonal treatment in transgender people. A first paper on the effects on meningioma is published and a studies on breast cancer and on cardiovascular disease are forthcoming.

Together, these studies aim to better understand the effects and side effects of treatment, and to develop and improve quality of care for individuals with gender dysphoria.

### Breast development in transgender persons

The topic of Christel de Blok's PhD research is twofold: on the one hand she studies breast care in transgender persons and on the other hand she investigates systemic symptoms in women with silicone breast implants. Within the transgender health care, the focus is on breast development in transwomen (male-to-female transgender persons), breast atrophy in transmen (female-to-male transgender persons), breast cancer in both transwomen and transmen, and the prevalence of breast augmentation in transwomen. In 2017 the first manuscript of this research in breast care in transgender persons was published in the Journal of Clinical Endocrinology and Metabolism. In this study we investigated breast development in transwomen during the first year of hormone treatment. We observed that breast development occurred predominately in the first six months of therapy, after which the growth stabilized to almost zero. Breast growth was modest demonstrated by a bra cup size of less than an AAA cup in most transwomen (48.7%). No clinical or laboratory parameters were identified to predict breast development. The biggest limitations of this study were the measurement method used (thorax circumferences) and the fact that this study only reported objective outcomes of breast development which says nothing about the satisfaction with the gained breast growth of the transwomen themselves. Therefore, we designed a new study to investigate breast development during hormone treatment, in which we collect data using 3D imaging of the breast to be able to measure breast volumes. Besides that, we also incorporated a questionnaire to gain more insight in the satisfaction with breast growth during hormone treatment. The inclusion of this study is ongoing and we expect to be able to present the results in the first half of 2019. We believe that breast development in transwomen is an important part of their transition, since breast development is a key feature of feminization. Optimization of breast development using research is not only of interest of transwomen but has a broader





Christel de Blok and Martin den Heijer

impact as well. The discussion about reimbursed breast augmentation in transwomen is restarted recently, which not only has consequences for the healthcare budget in the Netherlands, but also starts an ethical discussion because non transgender women with a small cup size could feel subordinated because they have to pay their breast augmentation themselves.

If we gain more knowledge about the physiology of breast development during hormone treatment and if we could detect predicting factors to gain good breast development, which we ideally could influence, than we might be able to optimize the current treatment and minimize additional (surgical) treatment.

## Interventions that target hepatic diacylglycerol accumulation and/or PKC activation for the prevention and treatment of insulin resistance?

Cell Rep. 2017 Jun 6;19(10):1997-2004

Kasper ter Horst and Mireille Serlie

### The interaction between body weight, energy metabolism and the brain

The laboratory of Dr. Mireille Serlie focuses on translational research on 1) the pathophysiology of obesity-related metabolic diseases, including insulin resistance and fatty liver disease and 2) the role of the brain in food intake and glucose metabolism in lean versus obese humans. We combine metabolic studies with molecular analysis in insulin-sensitive tissues as well as neuroimaging (the latter in collaboration with the departments of Nuclear Medicine and Radiology). This allows us to study the interaction between body weight, energy metabolism and the brain. This bench to bedside and bedside to bench approach is possible because of a close collaboration with the La Fleur Lab and other international collaborators. In 2017, we contributed to advancing our understanding of insulin resistance by demonstrating that hepatic protein kinase C Epsilon activation is important for **lipid-mediated insulin resistance** in humans; that adipose tissue insulin resistance can be **reliably quantified** from simple blood measurements in humans; that fructose ingestion **reduces insulin resistance**, is **associated with non-alcoholic fatty liver disease** (NAFLD) and acutely stimulates **fibroblast growth factor 21**, a novel hormone with beneficial effects on glucose, lipid, and energy metabolism. The brain has emerged as an important regulator of metabolism and rodent studies showed that serotonin and dopamine signaling is involved in food intake and reward. We **recently** showed that the **brain dopaminergic system is disturbed in obesity** in humans, a phenomena that was **partially reversed by surgery-induced weight loss**. We also reported on reduced **serotonin transporter availability** in the diencephalon of insulin-resistant obese subjects as well as a timing of caloric intake-dependent effect on **brain dopaminergic and serotonergic systems during diet-induced weight loss**. Finally, we established a **role for dopamine and the nucleus accumbens** in the control of glucose metabolism by performing studies in humans (AMC) and mice (Yale). All together, these studies show

that the brain might be a potential therapeutic target in the treatment of insulin resistance and obesity.

Some of our ongoing projects include a big-data analysis of fluxomics, metabolomics, and transcriptomics to explore the mechanisms of insulin resistance and the metabolic syndrome in obese humans (within the RESOLVE consortium); a study in humans on the pathogenesis and metabolic consequences of NAFLD (in collaboration with Prof. G.I. Shulman's lab at Yale) as well as the effect of fat and sugar on brain reward pathways and insulin resistance in lean and obese humans. We are excited to find out what the remaining months of 2018 may bring.

### Lipid-mediated insulin resistance

Insulin resistance is a pathological state, defined by diminished biological responses to the hormone insulin. It is the major contributor to the metabolic complications of obesity, including hyperglycemia and dyslipidemia, because it results in impaired regulation of blood glucose concentrations, cellular glucose metabolism, and lipid metabolism. The accumulation of lipids in liver cells, which is often referred to as non-alcoholic fatty liver disease (NAFLD), has been implicated in the development of insulin resistance. Rodent studies have shown that an important underlying mechanism for hepatic insulin resistance involves hepatic diacylglycerol-induced protein kinase C (PKC) activation, but the mechanisms for lipid-mediated insulin resistance in humans were largely unknown. In collaboration with researchers from the AMC and Yale University Medical School, Kasper ter Horst **showed** that the presence of hepatic steatosis in obese subjects was associated with hepatic, adipose tissue, and peripheral insulin resistance; however, intrahepatic triglycerides were not strictly sufficient or essential for hepatic insulin resistance, suggesting that other factors must be involved. In an attempt to determine the molecular mechanisms that link fatty liver disease to impaired insulin action, liver biopsies were collected



from a subset of obese subjects. Here, subjects with hepatic insulin resistance were characterized by increased diacylglycerol content in the cytosolic fraction of hepatocytes. Diacylglycerols are metabolically active lipids composed of glycerol and two fatty acid chains. Diacylglycerol species in the membrane fraction or ceramides, which had previously been implicated in hepatic insulin resistance, were unaltered in obese humans with hepatic insulin resistance. Importantly, diacylglycerol-associated insulin resistance was strongly associated with hepatic PKC $\epsilon$  activation, as reflected

by PKC $\epsilon$  translocation from the cytosol to the plasma membrane. Activated PKC $\epsilon$ , in turn, may inhibit the hepatic insulin signaling cascade, thereby contributing to impaired insulin action and the development of glucose intolerance/hyperglycemia. These results thus demonstrated an important human mechanism for lipid-mediated insulin resistance, supporting the development of novel interventions that target hepatic diacylglycerol accumulation and/or PKC $\epsilon$  activation for the prevention and treatment of insulin resistance and type 2 diabetes.



# AG&M Best Publication 2017

During the AG&M symposium “Nutrition” on Wednesday March 28th 2018, the battle for best AG&M publication 2017 took place. Six nominees, Sandra van Brunschot, Kasper ter Horst, Davor Slijepcevic, Marijn Warners, Irina Milanova (for Yuanqing Gao) and Anneloes Opperhuizen pitched their publication in 5 minutes each. The audience voted for Anneloes Opperhuizen as winner of the battle with her publication entitled *“Light at night acutely impairs glucose tolerance in a time-, intensity- and wavelength-dependent manner in rats”*.

Anneloes Opperhuizen performed her PhD-research in the group of Prof. Dr. Andries Kalsbeek. This research group furthermore consists of the PhD’s Paul de Goede, Satish Sen, Lamis Saad, Fernando Cazarez Marquez,

Anayanci Masis Vargas and Eleni Angelopoulou, technician Wayne Ritsema, students Rick Hogenboom, Ratna Mellema, Anne Kappert and HLO interns Eva van Sambeek and Nicole Plomp. Research in the group focusses on the role of the hypothalamus in the neuro-endocrine regulation of energy metabolism, with a focus on glucose metabolism. The hypothalamus rules those things in life that really matter, such as sex and food, love and aggression, and last but not least the hypothalamus controls the rhythm of our life. To unravel the mechanisms of hypothalamic integration they especially study the hypothalamic biological clock and how it enforces its molecular rhythms via the autonomic nervous system and circadian control of hormone rhythm onto daily physiology and behavior.

## **Light at night acutely impairs glucose tolerance in a time-, intensity- and wavelength-dependent manner in rats**

In the article ‘Light at night acutely impairs glucose tolerance in a time-, intensity- and wavelength-dependent manner in rats’ published in *Diabetologia* (2017), we describe a series of experiments challenging glucose regulation after light exposure at night. Due to the widespread use of electronic devices, as well as, the large number of people doing shiftwork, an increasing number of people are frequently exposed to light at night. Light is an essential input signal to

the mammalian body, as it synchronizes the internal biological clock system with external time. Light entering via the eyes and the brain helps to adjust bodily functions to the time of day to optimally prepare the body for daily challenges. Exposure to light at night is an unnatural time for the body to deal with incoming light signals and this has been correlated with adverse health conditions, including an increased risk of diabetes type 2 and sleep disorders.



Anneloes Opperhuizen



Group Kalsbeek

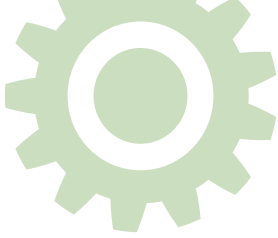
Glucose metabolism is a tightly regulated homeostatic, but also clock-controlled process. This mechanism is coordinated by the brain through an interplay of several organs including the liver, skeletal muscle and the pancreas. Previous studies in our lab demonstrated that exposure to 1 hour of light at night affected gene expression in the liver of rats. We observed upregulation of Phosphoenolpyruvate carboxykinase (Pepck) mRNA, which codes for an enzyme essential during glucose production. Consequently we hypothesized that short exposure to light at night could affect glucose metabolism. Therefore we subjected male Wistar rats to intravenous glucose tolerance, or insulin sensitivity tests (IVGTT/IVITT). By this method the tolerance of the body to an infused bolus of glucose or insulin is determined by measuring the speed by which plasma glucose normalize again. Increased blood glucose levels indicate impaired glucose tolerance, which is also found in human prediabetic patients.

The first experiment included a number of IVGTTs and IVITTs under dark control or light exposure conditions at different times during the night. Light exposure lasted for two hours, with the tolerance test being executed during the second hour. We found that exposure to light at night immediately caused stronger increases in blood glucose, and thus glucose intolerance. At the two different time points during the night we observed different responses, in the early night insulin levels were equal in both lighting conditions, but insulin levels

were increased by light at the end of the night. This time-of-day effect suggests that the biological clock system plays a role in the light mediated effect on glucose metabolism.

In the second and third experiment we explored the importance of characteristics of the light exposure on glucose tolerance and locomotor activity. Earlier studies have shown that brighter light or light enriched with the blue wavelength, can be more disruptive for biological functions such as sleep. We experimented with four different intensities (ranging from 5 to 150 photopic lux; experiment 2) and four different colors (white, red, green and blue; experiment 3). Increasing intensity caused increased glucose intolerance with a threshold between 5 and 20 lux. Surprisingly, rats exposed to red and blue light did not show affected glucose tolerance, whereas white and green light did induce glucose intolerance. All colors, except red light induced a decrease in locomotor activity, proving that the rats observed the light and demonstrated a behavioral response. These data suggest the importance of specific retinal cells and possibly specific eye-brain-periphery pathways to transport light signals.

In conclusion, this article describes the potential of an ordinary habit, the use of light at night, to disrupt a biologically extremely important function; glucose regulation. This awareness is important for the millions of shiftworkers frequently exposed to conditions including exposure to light at night.



## AG&M Grants 2017

In 2017, AG&M awarded 2 types of grants to young talent. The AG&M international student research fellowship (20 kEuro) meant for (bio-)medical students (in their MSc-program or just graduated) to participate in a research internship for a year at an international top institute and the AG&M PhD talent development grant (280 kEuro) for postdocs (within 5 years after obtaining their PhD) to stimulate the successful transition from postdoc to group leader.

### The AG&M international student research fellowship



#### Jelmi uit de Bos

After finishing my bachelor's degree in Biomedical Sciences at the University of Amsterdam, I continued with a Masters program focusing on biochemistry and metabolic diseases. My interest in biomedical research was sparked soon after starting my bachelor studies, where I followed a wide variety of courses on topics such as molecular biology, genetics, immunology and microbiology. During my study I participated in the research honors program, where I designed and executed my own research plan in the group of Dr. Riekelt Houtkooper at the Academic Medical Centre in Amsterdam. Here, I developed a growing interest in metabolism. Part of my current masters program is to participate in two research internships. My first internship I performed in the group of Benjamin Rowland at the Netherlands Cancer Institute.

#### *The AG&M international student research fellowship allowed me...*

... to perform my second research internship for a year in the group of David Sabatini at the Whitehead Institute for Biomedical Research in Cambridge, US. In September 2017 I started my internship, where I got the chance to work independently on a project to characterize a hit from a genetic screen. The hit is a mitochondrial transmembrane protein that is hypothesized to play a role in one-carbon metabolism. One carbon (1C)-metabolism is a central pathway that is essential for many cellular functions, including nucleotide synthesis, redox balance and epigenetic maintenance. 1C metabolism is highly conserved throughout evolution and comprises a set of reactions that depend on the co-factor tetrahydrofolate (THF) to transfer 1C units to a diverse set of targets. Despite its important role in metabolism and cell function, several aspects of 1C metabolism remain unknown.

So far I have learnt many different molecular and biochemical techniques, but more importantly, this internship has taught me how to do research at one of the highest levels imaginable. Research here goes incredibly fast and there are many exciting projects ongoing. I am very grateful for this opportunity and think this experience has been crucial in my research career. It has prepared me most for entering a PhD program in the future.



## The AG&M PhD talent development program



### Daniel Miedema

After a study in physics and specialization in biophysics during my PhD, I started working on oncology during my postdoc at the AMC. I am focusing my research on cancers of the gastrointestinal (GI) tract, with a particular interest in the development and growth of colorectal cancer. I find it very exciting to translate quantitative tools from physics and mathematics to applications in oncology. I believe both mathematical modelling and “big” data driven approaches can be very useful in cancer research.

#### *The AG&M talent development program allows me...*

... to start building a team that studies cancer with a quantitative approach within the institute. Together with PhD student Tom van den Bosch, which was funded through the AG&M talent development program, I am currently working on projects ranging from the earliest signs of abnormal cell growth in healthy GI tissues, to development of personalized treatment for patients diagnosed with cancer. We develop stochastic models of cell growth that can be applied to each phase of the disease. We work in close collaboration with wet-lab biomedical researchers to derive the fundamental dynamics of tissue growth during homeostasis, inflammation and in established cancers by combining experimental data with stochastic modelling and simulations.

More recently, we started collaborating with GI surgeons to predict which patients have a high risk of complications after undergoing surgery for colorectal cancer and thus require extra attention. Here, we use large sets of clinical data to stratify patients based on characteristics such as age and comorbidities. In the next few years we hope our work will contribute to a better understanding of cancer development and a more personalized treatment of patients diagnosed with cancer.



# AG&M Events 2017

JANUARY

26<sup>th</sup>

## AG&M kick-off party

*Museumcafé Mokum, Amsterdam*



As of January 1st, 2017 the AG&M research institute is officially operational. To celebrate this, the institute organized a kick-off event on Thursday January 26th for the AG&M researchers to get to know each other in an informal manner.

Gerd Bouma, AG&M director from the De Boelelaan campus, started the evening in Museumcafé Mokum with an elucidation of the AG&M institute formation history. During the dinner thereafter, the AG&M senior investigators met their colleagues. Following the starter, the comedian Joop Vos playfully illustrated the essence of the research institute, collaboration: *“Jullie zijn de Barack Obama’s voor het onderzoek. De Erica Terpstra’s voor alle disciplines onderling. De Yuri van Gelders voor het uitzetten van de lijnen. Ambassadeurs van de samenwerking”*. This led to plenty of conversation during the rest of the dinner.

After dinner, the AG&M Post Docs and PhD-students joined. Stan van de Graaf, AG&M director from the

Meibergdreef campus, welcomed them. His message was clear: *“The AG&M research institute is a network organization for all researchers in the gastroenterology and metabolic field. Later also an advertisement for your research to the outside world. How are we going to achieve this? And with “we”, I mean not only Gerd and me, but all of you. We are the AG&M research institute. The institute that is you.”*

With a drink and a snack, the rest of the evening could be spend getting to know unknown colleagues. Joop Vos mediated this process by forming a meeting circle. With their hand on their chest the somewhat astonished crowd sang the specially written AG&M battle song: *“Waar de samenwerking almaar zal*





Comedian Joop Vos (joopvos.com) playfully mediates the acquaintance process.



*bloeien. Waar we ons manifesteren als een goed geoliede tandem. Waar de resultaten tot in de hemel groeien. Daar klopt het hart van het AG&M".* Furthermore, the pub quiz provided some essential knowledge to better understand colleagues from the

other side of the Amstel. It was a successful evening in which people got to know each other and the first steps were taken towards new collaborations between researchers at both sides of the Amstel that will create a stronger national and international scientific position.

APRIL

20<sup>th</sup> | 21<sup>st</sup>

## AG&M annual meeting

*Bilderberg Hotel 't Speulderbos, Garderen*



Although there was already an semi-official AG&M PhD-students retreat in 2016, the first official AG&M retreat took place on April 20th and 21st 2017 at the Bilderberg Hotel 't Speulderbos in Garderen. With a lot of interesting topics of more than 80 PhD-students and 35 group leaders, it was a program suited for everyone from the AG&M institute. Part of the program was combined, part of it was separate for PhD-students and group leaders.

This year the committee decided to create parallel sessions within the program of the PhD-students on specific topics which resulted in more time for each speaker. Four invited speakers showed us their very diverse research experiences. On Thursday, Chris Mulder, (former) head of the gastroenterology and hepatology department of the VUmc, talked about

his 40 years experiences as a medical doctor. On Friday, Susanne La Fleur showed us the link between neurobiology and energy metabolism and Fleur Bouwer showed the magic of music. Editor-in-chief Robert Brierley took us, in a plenary session with the PIs, behind the scenes of Lancet Gastroenterology & Hepatology. In the parallel program of the group



leaders, the investigators presented their research lines and discussed the future of AG&M. As surprise act, illusionist Jan Reinder was invited who made the impossible possible during the Thursday evening program. With a lot of networking, including a great party, and the PI parallel sessions, this first official AG&M retreat 2017 was a great success!



#### Awards AG&M PhD-students retreat 2017

**Best Abstract:** Paul de Goede – Timing of feeding behavior regulates rhythms in the muscle molecular clock and glucose tolerance

**Best Pitches:** Ntsiki Held – Fluxomic tools for characterization of metabolic reprogramming upon brown adipose tissue activation, Melek Simsek – Paternal and maternal fertility and pregnancy outcomes in IBD patients exposed to thiopurines, Annefleur Koopen – Effect of Fecal microbiota Transplantation combined with Mediterranean Diet on insulin sensitivity in subjects with metabolic syndrome: FATMED trial

**Most contributing participant:** Daan Brinkman

SEPTEMBER



## AG&M symposium: “Gut inflammation and Metabolism”

Desmet Studio's, Amsterdam



On September 8th 2017, ~70 researchers came together at the Desmet Studio's in Amsterdam for the “Gut inflammation and Metabolism” symposium, initiated by AG&M principal investigator Prof. dr. Wouter de Jonge.

AG&M researchers presented their work on gut inflammation and metabolism. Prof. dr. Max Nieuwdorp and PhD-students Annick Hartstra and Judith Zeevenhooven talked about their data on metabolic syndrome, Prof. dr. Geert D'Haens and researchers Pim Koelink (Post Doc), Mohammed Ghiboub (PhD-student) and Joep Grootjans (Post Doc) spoke about the ins and outs of inflammatory bowel disease and Dr. Dries Budding deliberated on how to predict the course and optimal treatment of

*C. difficile* infection.

As special guests, Prof. dr. Wayne Lencer and Dr. Ivan Zanoni from Children's Hospital Boston, USA, joined the symposium to share their data on how endogenous ligands control innate immune cell metabolism, and Dr. James Kinross from Imperial College London, UK, enlightened the audience on novel methodologies for studying metabolic signaling in gut inflammation.







Amsterdam Gastroenterology & Metabolism	
<h1>AG&amp;M symposium</h1> <h2>“Gut inflammation and metabolism”</h2> <h3>FRIDAY SEPTEMBER 8th 2017</h3> <p>08:45 – 16:30h Including lunch and drinks afterwards</p> <p><b>Location:</b> Desmet Studio's Amsterdam Plantage Middenlaan 4a, Amsterdam</p> <p><b>Confirmed speakers:</b> Prof. dr. Max Nieuwdorp, VUmc/AMC Prof. dr. Geert D'Haens, AMC Dr. James Kinross, Imperial College London Dr. Ivan Zanoni, Children's Hospital Boston Dr. Dries Budding, VUmc</p> <p><i>FMT-microbiome</i> <i>Metabolomics</i> <i>Inflammatory Bowel Disease</i> <i>Clostridium difficile infection</i> <i>Innate immune cell metabolism</i> <i>Metabolic syndrome</i></p> <p> <a href="http://www.amsterdam-gastroenterology-and-metabolism.org">www.amsterdam-gastroenterology-and-metabolism.org</a> </p>	
PROGRAM	
09:00 - 09:15h:	Opening: Stan van de Graaf / Wouter de Jonge
09:15 - 10:30h <b>SESSION 1: metabolic syndrome</b>	
Max Nieuwdorp Annick Hartstra:	<i>FMT-microbiome related changes in serotonin and glucose metabolism (preliminary data).</i>
Judith Zeevenhooven:	<i>FMT-microbiome in IBS (trial and rationale).</i>
10:30 - 11:00h:	Coffee/Tea
11:00 - 12:30h <b>SESSION 2: inflammatory bowel disease</b>	
Geert D'Haens Pim Koelink:	<i>Improving efficacy of anti-TNF in IBD.</i>
Mohammed Ghiboub:	<i>SP140 is a novel mediator of macrophage activation in inflammatory bowel disease.</i>
Joep Grootjans:	<i>The interplay between epithelium and immune cells in ER stress-induced intestinal inflammation.</i>
12:30 - 13:30h:	Lunch
13:30 - 15:00h <b>SESSION 3: Immuno-metabolism, metabolomics and microbiome</b>	
Ivan Zanoni:	<i>Endogenous ligands control innate immune cell metabolism.</i>
James Kinross:	<i>Novel methodologies for studying metabolic signalling in gut inflammation.</i>
Dries Budding:	<i>Predicting the course and optimal treatment of C.difficile infection by rapid microbiota profiling.</i>
15:00 – 15:05h:	Closure: Stan van de Graaf / Wouter de Jonge
15:05 – 16:30h:	<b>DRINKS</b>

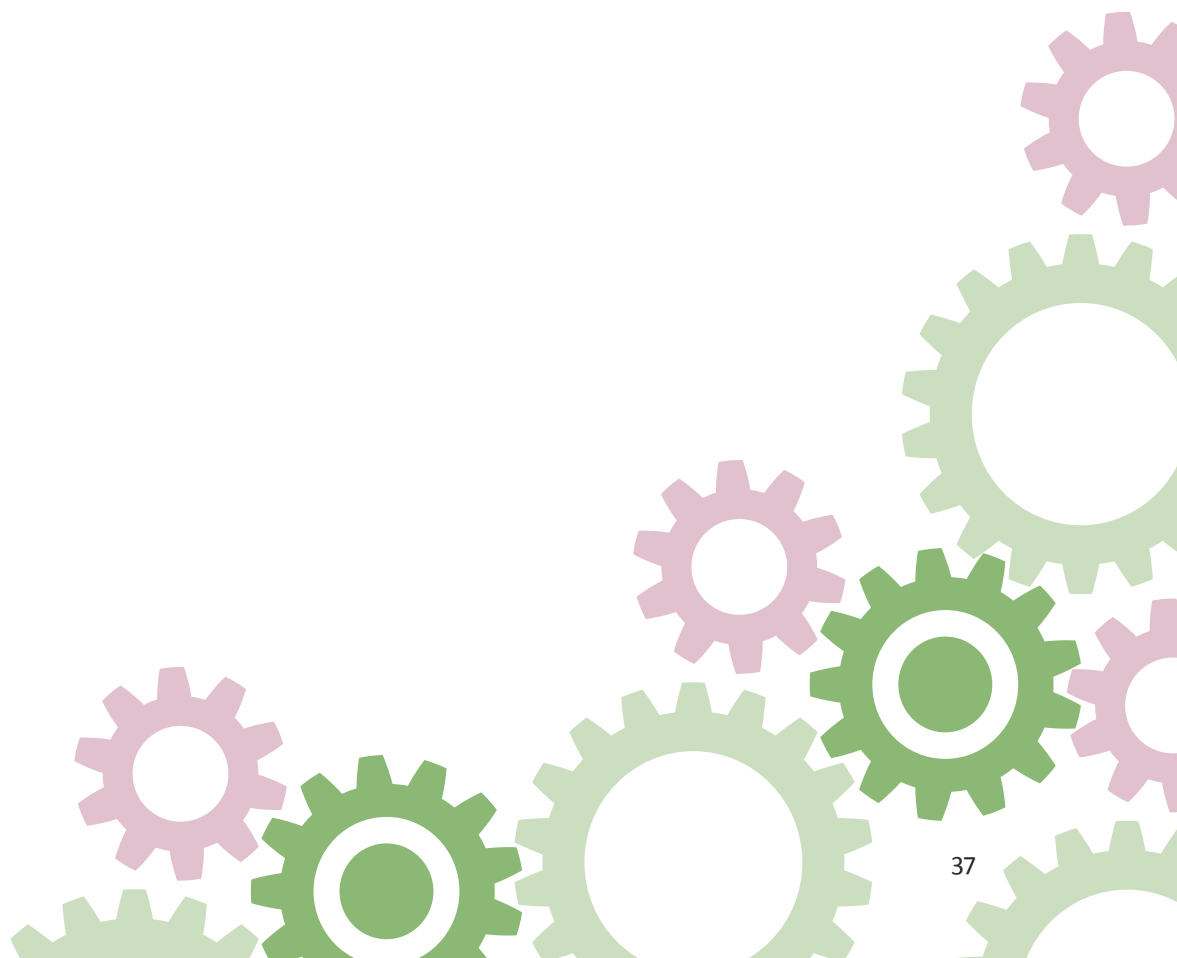
## AG&M Tager Lectures

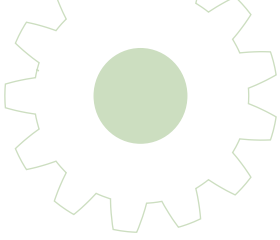
The AG&M research institute has a bimonthly seminar series in the Amsterdam UMC, location AMC, focused on metabolism; the Tager Lecture, called after Professor Joseph Tager.

Joseph Tager made important contributions to Fabry, Pompe and Gaucher disease and had a major impact on our understanding of peroxisomal diseases. He was chairman of the Biochemistry Department at the University of Amsterdam (1980-1991).

The Tager Lecture series is organized by AG&M PI's Riekelt Houtkooper, Susanne La Fleur (as of 2018), Stan van de Graaf and Noam Zelcer. Suggestions for future speakers for the Tager lecture are always welcome.

<b>APRIL</b>	 <b>13<sup>th</sup></b>	<p><b>Prof. Dr. Kieran Clarke</b>  <i>Department of Physiology, Anatomy &amp; Genetics University of Oxford</i></p>	<p>Exogenous ketones: A new approach to human health and disease</p>
<b>MAY</b>	 <b>11<sup>th</sup></b>	<p><b>Dr. Bart van de Sluis</b>  <i>Center for Liver, Digestive and Metabolic Diseases, RUG Groningen</i></p>	<p>Sorting the interactome of the endosomal trafficking machinery to preserve metabolic pathways in the liver</p>
<b>JUNE</b>	 <b>29<sup>th</sup></b>	<p><b>Prof. Dr. Lonny R. Levin</b>  <i>Department of Pharmacology Weill Cornell Medical College, NY, USA</i></p>	<p>Intracellular cAMP microdomains</p>
<b>OCTOBER</b>	 <b>5<sup>th</sup></b>	<p><b>Prof. Dr. Hans Romijn</b>  <i>Department of Internal Medicine, AMC, Amsterdam, The Netherlands</i></p>	<p>Direct versus indirect effects of insulin in peripheral tissues</p>
<b>NOVEMBER</b>	 <b>2<sup>nd</sup></b>	<p><b>Dr. Maaike H. Oosterveer</b>  <i>Department of Pediatrics, University Medical Center Groningen, The Netherlands</i></p>	<p>Hepatic glucose sensing: from metabolic control to pathophysiology of disease</p>
<b>DECEMBER</b>	 <b>13<sup>th</sup></b>	<p><b>Prof. Dr. Zach Gerhart-Hines</b>  <i>Center for Basic Metabolic Research, Copenhagen, Denmark</i></p>	<p>Cardiolipin Synthesis Governs Systemic Energy Homeostasis through Thermogenic Fat Mitochondria</p>





# AG&M Numbers and Facts 2017

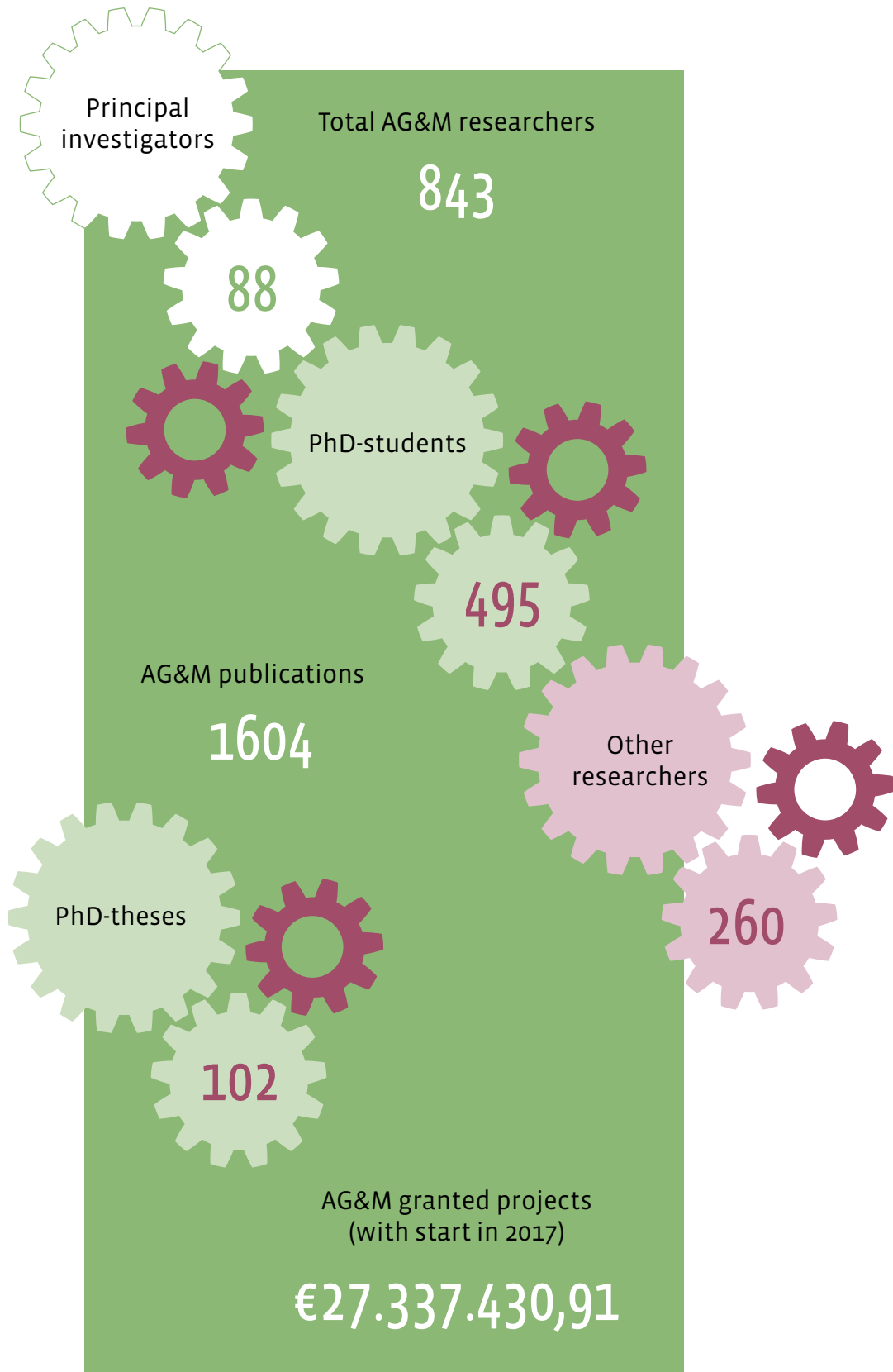
## AG&M finances 2017

In 2017, the AG&M research institute had €500.000,00 (€250.000,00 from board of directors VUmc and €250.000,00 from board of directors AMC) to spend. In the table below is shown how this money was

budgeted and spend. Most of the 2017 budget was used for the AG&M grants (The AG&M international student research fellowship and The AG&M PhD talent development program).

	Budgeted	Expenses
AG&M grants	€ 320.000,00	€ 300.000,00
Personnel	€ 75.000,00	€ 71.559,68
Meetings	€ 80.000,00	€ 37.580,32
Miscellaneous	€ 25.000,00	€ 7.125,97
<b>Total</b>	<b>€ 500.000,00</b>	<b>€ 416.265,97</b>

AG&M numbers 2017



**AG&M researchers per research program**

	<b>Principal investigators</b>	<b>PhD-students</b>	<b>Other researchers</b>	<b>Total AG&amp;M researchers</b>
Re-generation and cancer of the digestive system	19,0	130,5	54,3	<b>203,8</b>
Digestive immunity	22,0	146,5	72,8	<b>241,3</b>
Endocrinology, metabolism and nutrition	35,0	180,2	90,8	<b>305,9</b>
Inborn errors of metabolism	12,0	37,8	42,3	<b>92,1</b>

**AG&M publications per research program**

	<b>Publications</b>	<b>PhD-theses</b>
Re-generation and cancer of the digestive system	426,2	54,3
Digestive immunity	443,3	72,8
Endocrinology, metabolism and nutrition	555,5	90,8
Inborn errors of metabolism	179,0	42,3

The information about researchers and the research output published by researchers at Amsterdam UMC in 2017 was collected by the Medical Library (AMC) and Research Support (VUmc) and complemented and validated by the departments. Based on information provided by the Research Institutions the researchers

and research output has been affiliated to Research Institutions and research programs.

The publications, current PhD-students, PhD-theses and grants were selected if at least one of the authors / (co)supervisors / project leaders belonged to the research institute in 2017.



**Appointed professors 2017**



**Prof. dr. M.M. van Weissenbruch**

*Pediatrics, in particular Neonatology*



**Prof. dr. M.I. van Berge Henegouwen**

*Gastrointestinal Surgery, specialising in oesophageal and gastric surgery*



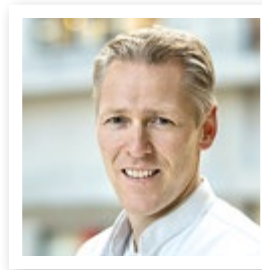
**Prof. dr. S.E. la Fleur**

*Neurobiology of Energy Metabolism*



**Prof. dr. E.A.J. Reits**

*Cellular Imaging*



**Prof. dr. M.G.H. Besselink**

*Surgery, specialising in pancreatic and hepatobiliary (HPB) surgery*



**Prof. dr. L. Vermeulen**

*Molecular Oncology*



**Prof. dr. J.W. Groothoff**

*Pediatrics, in particular Nephrology*

**Did you know that...**

... AG&M PI Marc Besselink published no less than 68 papers in 2017.

... AG&M PI Christina Vandenbroucke-Grauls has been appointed "Ridder in de Orde van de Nederlandse Leeuw" for her outstanding work on infectious diseases and medical microbiology (6-10-2017).

... the electronic nose (eNose) can detect differences in fecal gas between smokers and non-smokers. This was investigated by AG&M researchers Nanne de Boer and Tim de Meij who received media

attention in 7 different sources on this topic (parool.nl, telegraaf.nl, rtlnieuws.nl, blikopnieuws.nl, kijkmagazine.nl, cosmopolitan.com, nu.nl).

... AG&M PI Louis Vermeulen is, at age 33, the youngest appointed professor at the Amsterdam UMC.

... you don't always have to complete your antibiotics course, as explained by AG&M PI Christina Vandenbroucke-Grauls on radio (BNR nieuwsradio, 27-7-2017) and television (NOS nieuwsuur, 27-7-2017)

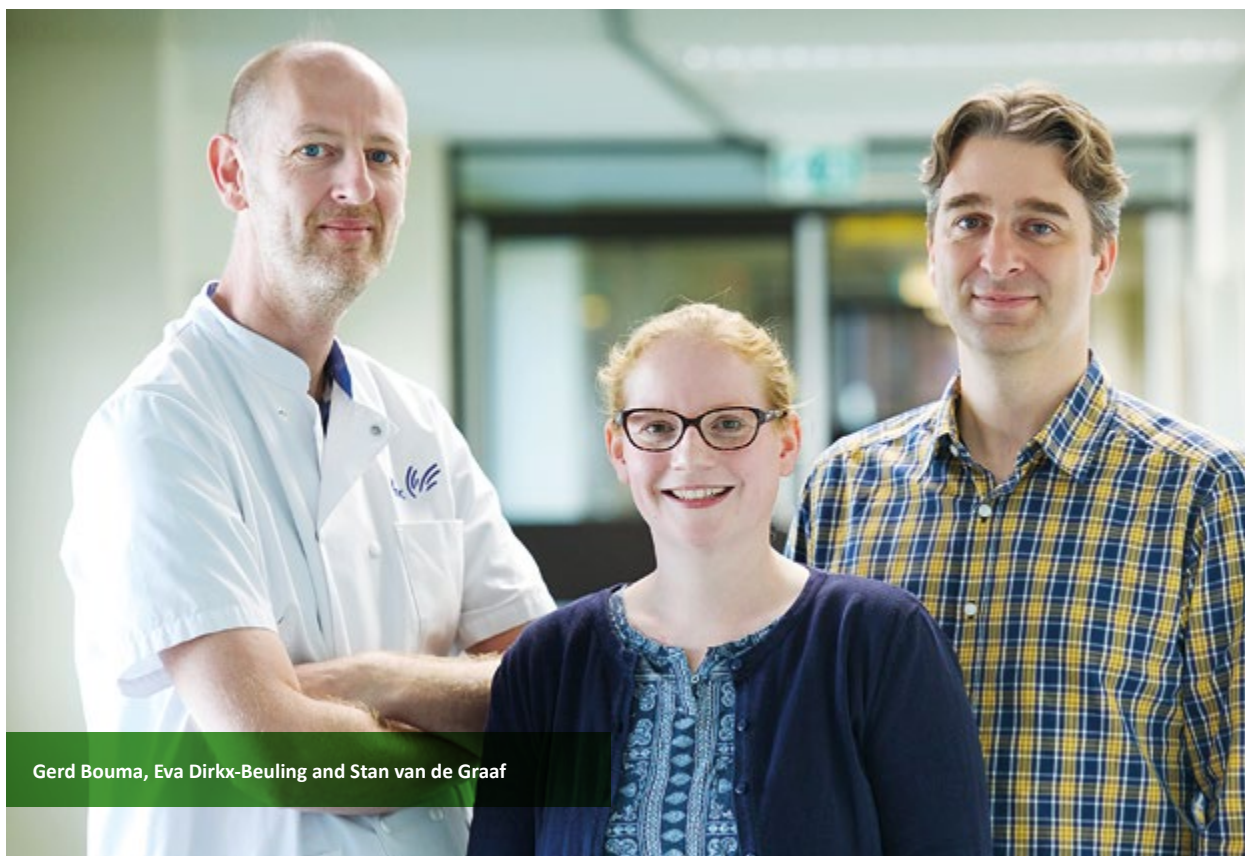


# Future perspectives for the AG&M research institute

The AG&M research institute achieves her mission by promoting the quality and visibility of the research in our institute through a focus on **10 specific aims**.

In 2017, the first year of the AG&M existence, considerable time and resources have been devoted to building a foundation necessary to develop and improve the quality of the institute. The AG&M events (Kick-off party, AG&M retreat, AG&M symposium, AG&M Tager Lectures) and grants were organized in a manner to contribute to the following aims:

1. Familiarize the researchers of the Amsterdam UMC, location VUmc and AMC, with each other and promote a spirit of common purpose.
2. Create an atmosphere of intellectual excitement in which researchers believe in the possibility to extend the horizon of our understanding of biology and disease and to make important contributions to medicine of the 21st century.
3. Identify the key research questions for the coming decade and actively work within the AG&M research programs to address these questions.
4. Promote a multidisciplinary approach to research within the institute between different research programs and between scientists at the bench and bedside.
5. Focus on those areas of research where the full chain of translational research is at an international top level.
6. Talent development: recruit and train the next generation of excellent researchers for research programs of AG&M.  
  
Furthermore, the AG&M directors, AG&M research board and prominent AG&M researchers consistently lobby to:
7. Increase quality of the core facilities required for the research at the highest international academic level. Research of the AG&M institute is dependent on all existing core facilities of the Amsterdam UMC. The core facilities of the Amsterdam UMC require a budget that is well beyond the budget available for the AG&M institute. The AG&M researchers feel that the core facilities have been systematically underfunded in the past years and therefore consistently urge the board of directors of the Amsterdam UMC to considerably increase funding of the existing core facilities and create novel core facilities.



Gerd Bouma, Eva Dirx-Beuling and Stan van de Graaf

The coming years, AG&M will continue to investigate in anchoring and expanding bonds and common goals and actively stimulating researchers to be excited by their work and believe in being able to tackle important clinical and scientific questions by evaluating and developing the AG&M program.

Furthermore, AG&M will extend its horizon by investing time, effort and resources into the following aims:

8. Collaborate closely with colleagues of the top of our international academic field and develop stable partnerships with their institutes.

AG&M will identify existing collaborations that include exchange programs between major top international centers and AG&M researchers. The AG&M will help strengthen these collaboration by both providing organizational and financial support

9. Provide an attractive platform for preclinical and clinical development for commercial entities active in our disease areas.

One of the important goals of the AG&M institute is to solidify and expand existing ties and collaborations with partners in industry.

10. Develop a branding & communication strategy, which is used to target the general public, patients, academic colleagues, charities and industry. The quality of research is highly dependent on how well findings are translated into practical use of the (worldwide) general public. Therefore, communication between the researchers and the rest of the world is essential.

Together with all AG&M members, we hope to develop the AG&M research institute in such a way that the institute is able to perform research that promotes healthy nutrition and metabolism, prevents or cures gastrointestinal, endocrine and inherited and acquired metabolic disease and improves the outcomes of our patients.

Gerd Bouma, *AG&M director*  
Stan van de Graaf, *AG&M director*  
Eva Dirx-Beuling, *AG&M policy officer*



# Amsterdam Gastroenterology and Metabolism